SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Combivir 150 mg/300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine and 300 mg zidovudine.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, capsule-shaped film-coated scored tablets engraved with "GXFC3" on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Combivir is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection (see section 4.2).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Combivir may be administered with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

Adults and adolescents weighing at least 30 kg: the recommended dose of Combivir is one tablet twice daily.

Children weighing between 21 kg and 30 kg: the recommended oral dose of Combivir is one-half tablet taken in the morning and one whole tablet taken in the evening.

Children weighing from 14 kg to 21 kg: the recommended oral dose of Combivir is one-half tablet taken twice daily.

The dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling and supported by data from clinical studies using the individual components lamivudine and zidovudine. A pharmacokinetic overexposure of zidovudine can occur, therefore close safety monitoring is warranted in these patients. If gastrointestinal intolerance occurs in patients weighing 21-30 kg, an alternative dosing schedule with one-half tablet taken thrice daily can be applied in attempt to improve tolerability.

Combivir tablets should not be used for children weighing less than 14 kg, since doses cannot be appropriately adjusted for the weight of the child. In these patients, lamivudine and zidovudine should be taken as separate formulations according to the prescribed dosing recommendations for these products. For these patients and for patients, who are unable to swallow tablets, oral solutions of lamivudine and zidovudine are available.

For situations where discontinuation of therapy with one of the active substances of Combivir, or dose reduction is necessary separate preparations of lamivudine and zidovudine are available in tablets/capsules and oral solution.

*Renal impairment***:** Lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance (see section 4.4). Therefore as dosage adjustment of these may be necessary it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe renal impairment (creatinine clearance ≤30 mL/min). Physicians should refer to the individual prescribing information for these medicinal products.

Hepatic impairment: Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. However, as dosage adjustments for zidovudine may be necessary, it is recommended that separate preparations of lamivudine and zidovudine

be administered to patients with severe hepatic impairment. Physicians should refer to the individual prescribing information for these medicinal products.

Dosage adjustments in patients with haematological adverse reactions: Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dL or 5.59 mmol/L or the neutrophil count falls below 1.0 x 10^9/L (see sections 4.3 and 4.4). As dosage adjustment of Combivir is not possible, separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual prescribing information for these medicinal products.

Dosage in the elderly: No specific data are available, however special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts (<0.75 x 10^9/L), or abnormally low haemoglobin levels (<7.5 g/dL or 4.65 mmol/L). Combivir is therefore contraindicated in these patients (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity reactions (see also section 4.8):

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see section4.8) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

Therefore the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- Ziagen should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen. (e.g. Kivexa, Trizivir, Triumeq)
- **Ziagen must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Ziagen after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with Ziagen for reasons of a suspected HSR, **Ziagen or any other medicinal product containing abacavir** (e.g. Kivexa, Trizivir, Triumeq) **must never be re-initiated**.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a

prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

- In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Ziagen tablets

Clinical description of abacavir HSR

Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, **although these reactions may occur at any time during therapy.**

Almost all HSR to abacavir include fever and/or rash. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms may lead **to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis** .

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy (see Section 4.8 Description of selected adverse reactions). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues ; these have predominantly concerned treatment with regimens containing zidovudine.The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleotide and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain.

Triple nucleoside therapy

In patients with high viral load (>100,000 copies/ml) the choice of a triple combination with abacavir, lamivudine and zidovudine needs special consideration (see section 5.1).

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when abacavir was combined with tenofovir disoproxil fumarate and lamivudine as a once daily regimen.

Liver disease

The safety and efficacy of Ziagen has not been established in patients with significant underlying liver disorders. Ziagen is not recommended in patients with moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with chronic hepatitis B or C virus

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Renal disease

Ziagen should not be administered to patients with end-stage renal disease (see section 5.2).

Excipients

Ziagen oral solution contains 340 mg/ml of sorbitol. When taken according to the dosage recommendations each 15 ml dose contains approximately 5 g of sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol can have a mild laxative effect. The calorific value of sorbitol is 2.6 kcal/g.

Ziagen oral solution also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or

residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving Ziagen or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Myocardial Infarction

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Ziagen, action should be taken to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

4.5 Interaction with other medicinal products and other forms of interaction

Combivir contains lamivudine and zidovudine, therefore any interactions identified for these individually are relevant to Combivir. Clinical studies have shown that there are no clinically significant interactions between lamivudine and zidovudine.

Zidovudine is primarily metabolised by UGT enzymes; co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure. Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters (OCTs); co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure.

Lamivudine and zidovudine are not significantly metabolised by cytochrome P_{450} enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral

protease inhibitors, non-nucleosides and other medicinal products metabolised by major P_{450} enzymes.

Interaction studies have only been performed in adults. The list below should not be considered exhaustive but is representative of the classes studied.

Drugs by Therapeutic Area	**Interaction** **Geometric mean change (%)** **(Possible mechanism)**	**Recommendation concerning co-administration**
ANTIRETROVIRAL MEDICINAL PRODUCTS		
Didanosine/Lamivudine	Interaction not studied.	No dosage adjustment necessary.
Didanosine /Zidovudine	Interaction not studied.	
Stavudine/Lamivudine	Interaction not studied.	Combination not recommended.
Stavudine/Zidovudine	In vitro antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs.	
ANTI-INFECTIVE PRODUCTS		
Atovaquone/Lamivudine	Interaction not studied.	As only limited data available the clinical significance is unknown.
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg thrice daily)	Zidovudine AUC ↑33% Atovaquone AUC ↔	
Clarithromycin/Lamivudine	Interaction not studied.	Separate administration of Combivir and clarithromycin by at least 2 hours
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	No Combivir dosage adjustment necessary, unless patient has renal impairment (See Section 4.2).

Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Zidovudine	Interaction not studied.	When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.
ANTIFUNGALS		
Fluconazole/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Fluconazole/Zidovudine (400 mg once daily/200 mg thrice daily)	Zidovudine AUC ↑74% (UGT inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin/Lamivudine	Interaction not studied.	Insufficient data to recommend dosage adjustment.
Rifampicin/Zidovudine (600 mg once daily/200 mg thrice daily)	Zidovudine AUC ↓48% (UGT induction)	
ANTICONVULSANTS		
Phenobarbital/Lamivudine	Interaction not studied.	Insufficient data to recommend dosage adjustment.
Phenobarbital/Zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	
Phenytoin/Lamivudine	Interaction not studied.	Monitor phenytoin concentrations.
Phenytoin/Zidovudine	Phenytoin AUC ↑↓	
Valproic acid/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Valproic acid/Zidovudine (250 mg or 500 mg thrice daily/100 mg thrice daily)	Zidovudine AUC ↑80% (UGT inhibition)	
ANTIHISTAMINES (HISTAMINE H1 RECEPTOR ANTAGONISTS)		

Ranitidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necessary.
Ranitidine/Zidovudine	Interaction not studied	
Cimetidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necessary.
Cimetidine/Zidovudine	Interaction not studied.	
CYTOTOXICS		
Cladribine/Lamivudine	Interaction not studied *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine	Therefore the concomitant use of lamivudine with cladribine is not recommended (see section 4.4)
OPIOIDS		
Methadone/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8). Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
Methadone/Zidovudine (30 to 90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑43% Methadone AUC ↔	
URICOSURIC		
Probenecid/Lamivudine	Interaction not studied.	As only limited

Probenecid/Zidovudine (500 mg four times daily/2mg/kg thrice daily)	Zidovudine AUC ↑106% (UGT inhibition)	data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
MISCELLANEOUS		
Sorbitol solution (3.2g , 10.2 g, 13.4 g)/ Lamivudine	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% Cmax ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of Combivir with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

Abbreviations: ↑ = Increase; ↓=decrease; ↔= no significant change; AUC=area under the concentration versus time curve; C_{max}=maximum observed concentration; CL/F=apparent oral clearance

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4).

Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with Combivir and any of these medicinal products is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.
Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole (see interaction information above relating to lamivudine and co-trimoxazole), aerosolised pentamidine, pyrimethamine and acyclovir at doses used in prophylaxis.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, both animal data as well as clinical experience in pregnant women should be taken into account.
Animal studies have shown toxicity to the developing embryo and foetus in rats, but not in rabbits (see section 5.3). Abacavir has been shown to be carcinogenic in animal models (see section 5.3). Clinical relevance in human of these data is unknown. Placental transfer of abacavir and/or its related metabolites has been shown to occur in human.

In pregnant women, more than 800 outcomes after first trimester exposure and more than 1000 outcomes after second and third trimester exposure indicate no malformative and foetal/neonatal effect of abacavir. The malformative risk is unlikely in humans based on those data.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues (see section 4.4).

Breast-feeding

Abacavir and its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk. There are no data available on the safety of abacavir when administered to babies less than three months old. It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

Studies in animals showed that abacavir had no effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse reactions have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination. For many of these events, it

is unclear whether they are related to lamivudine, zidovudine, the wide range of medicinal products used in the management of HIV disease, or as a result of the underlying disease process.

As Combivir contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity following concurrent administration of the two compounds.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of zidovudine (see section 4.4).

Treatment with zidovudine has been associated with loss of subcutaneous fat which is most evident in the face, limbs and buttocks. Patients receiving Combivir should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with Combivir should not be continued (see section 4.4).

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Lamivudine:

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic systems disorders
Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia
Very rare: Pure red cell aplasia

Metabolism and nutrition disorders
Very Rare: Lactic acidosis

Nervous system disorders
Common: Headache, insomnia
Very rare: Peripheral neuropathy (or paraesthesiae)

Respiratory, thoracic and mediastinal disorders
Common: Cough, nasal symptoms

Gastrointestinal disorders
Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea
Rare: Pancreatitis, rises in serum amylase

Hepatobiliary disorders
Uncommon: Transient rises in liver enzymes (AST, ALT)
Rare: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash, alopecia
Rare: Angioedema

Musculoskeletal and connective tissue disorders
Common : Arthralgia, muscle disorders
Rare: Rhabdomyolysis

General disorders and administration site conditions
Common: Fatigue, malaise, fever

Zidovudine:

The adverse reactions profile appears similar for adults and adolescents. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leukopenia. These occurred more frequently at higher dosages (1200-1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than 100/mm^3 (see section 4.4).

The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Common : Anaemia, neutropenia and leukopenia
Uncommon: Thrombocytopenia and pancytopenia (with marrow hypoplasia)
Rare : Pure red cell aplasia
Very rare : Aplastic anaemia

Metabolism and nutrition disorders
Rare : Lactic acidosis in the absence of hypoxaemia, anorexia

Psychiatric disorders
Rare: Anxiety and depression

Nervous system disorders
Very common : Headache
Common : Dizziness
Rare : Insomnia, paraesthesiae, somnolence, loss of mental acuity, convulsions

Cardiac disorders
*Rare :*Cardiomyopathy

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Rare : Cough

Gastrointestinal disorders
Very common : Nausea
Common : Vomiting, abdominal pain and diarrhoea
Uncommon : Flatulence
Rare : Oral mucosa pigmentation, taste perversion and dyspepsia. Pancreatitis

Hepatobiliary disorders
Common : Raised blood levels of liver enzymes and bilirubin
Rare : Liver disorders such as severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders
Uncommon : Rash and pruritus
Rare : Nail and skin pigmentation, urticaria and sweating

Musculoskeletal and connective tissue disorders
Common : Myalgia
Uncommon : Myopathy

Renal and urinary disorders
Rare: Urinary frequency

Reproductive system and breast disorders
Rare : Gynaecomastia

General disorders and administration site conditions
Common : Malaise
Uncommon : Fever, generalised pain and asthenia
*Rare :*Chills, chest pain and influenza-like syndrome

The available data from both placebo-controlled and open-label studies indicate that the incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with zidovudine.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited experience of overdosage with Combivir. No specific symptoms or signs have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects.

If overdosage occurs the patient should be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine, but enhance the elimination of the glucuronide metabolite. For more details physicians should refer to the individual prescribing information for lamivudine and zidovudine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside reverse transcriptase inhibitors, ATC Code: J05AF06

Mechanism of action

Abacavir is a NRTI. It is a potent selective inhibitor of HIV-1 and HIV-2. Abacavir is metabolised intracellularly to the active moiety, carbovir 5'- triphosphate (TP). *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Resistance

In vitro resistance

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro,* requiring multiple mutations for a clinically relevant increase in EC_{50} over wild-type virus.

In vivo resistance (Therapy naïve patients)

Isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline (45%) or only M184V or M184I selection (45%). The overall selection frequency for M184V or M184I was high (54%), and less common was the selection of L74V (5%), K65R (1%) and Y115F (1%). The inclusion of zidovudine in the regimen has been found to reduce the frequency of L74V and K65R selection in the presence of abacavir (with zidovudine: 0/40, without zidovudine: 15/192, 8%).

Therapy	Abacavir + Combivir[1]	Abacavir + lamivudine + NNRTI	Abacavir + lamivudine + PI (or PI/ritonavir)	Total
Number of Subjects	282	1094	909	2285
Number of Virological Failures	43	90	158	291
Number of On-Therapy Genotypes	40 (100%)	51 (100%)[2]	141 (100%)	232 (100%)
K65R	0	1 (2%)	2 (1%)	3 (1%)
L74V	0	9 (18%)	3 (2%)	12 (5%)
Y115F	0	2 (4%)	0	2 (1%)
M184V/I	34 (85%)	22 (43%)	70 (50%)	126 (54%)
TAMs[3]	3 (8%)	2 (4%)	4 (3%)	9 (4%)

1.Combivir is a fixed dose combination of lamivudine and zidovudine
2.Includes three non-virological failures and four unconfirmed virological failures.
3. Number of subjects with ≥1 Thymidine Analogue Mutations (TAMs).

TAMs might be selected when thymidine analogs are associated with abacavir. In a meta-analysis of six clinical trials, TAMs were not selected by regimens containing abacavir without zidovudine (0/127), but were selected by regimens containing abacavir and the thymidine analogue zidovudine (22/86, 26%).

In vivo resistance (Therapy experienced patients)

Clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. In a meta-analysis of five clinical trials where abacavir was added to intensify therapy, of 166 subjects, 123 (74%) had M184V/I, 50 (30%) had T215Y/F, 45 (27%) had M41L, 30 (18%) had K70R and 25 (15%) had D67N. K65R was absent and L74V and Y115F were uncommon (≤3%). Logistic regression modelling of the predictive value for genotype (adjusted for baseline plasma HIV-1 RNA [vRNA], CD4+ cell count, number and duration of prior antiretroviral therapies), showed that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at Week 4 ($p=0.015$) or 4 or more mutations at median Week 24 ($p\leq0.012$). In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, cause a high level of resistance to abacavir.

Baseline Reverse Transcriptase Mutation	Week 4 (n = 166)		
	n	Median Change vRNA (log_{10} c/ml)	Percent with <400 copies/ml vRNA
None	15	-0.96	40%
M184V alone	75	-0.74	64%
Any one NRTI mutation	82	-0.72	65%
Any two NRTI-associated mutations	22	-0.82	32%
Any three NRTI-associated mutations	19	-0.30	5%
Four or more NRTI-associated mutations	28	-0.07	11%

Phenotypic resistance and cross-resistance

Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple TAMs. Phenotypic cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants. The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir and antiretrovirals from other classes (e.g. PIs or NNRTIs) is unlikely.

Clinical efficacy and safety

The demonstration of the benefit of Ziagen is mainly based on results of studies performed in adult treatment-naïve patients using a regimen of Ziagen 300 mg twice daily in combination with zidovudine and lamivudine.

Twice daily (300 mg) administration:

- *Therapy naïve adults*

In adults treated with abacavir in combination with lamivudine and zidovudine the proportion of patients with undetectable viral load (<400 copies/ml) was approximately 70% (intention to treat analysis at 48 weeks) with corresponding rise in CD4 cells.

One randomised, double blind, placebo controlled clinical study in adults has compared the combination of abacavir, lamivudine and zidovudine to the combination of indinavir, lamivudine and zidovudine. Due to the high proportion of premature discontinuation (42% of patients discontinued randomised treatment by week 48), no definitive conclusion can be drawn regarding the equivalence between the treatment regimens at week 48. Although a similar antiviral effect was observed between the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤400 copies/ml; intention to treat analysis (ITT), 47% versus 49%; as treated analysis (AT), 86% versus 94% for abacavir and indinavir combinations respectively), results favoured the indinavir combination, particularly in the subset of patients with high viral load (>100,000 copies/ml at baseline; ITT, 46% versus 55%; AT, 84% versus 93% for abacavir and indinavir respectively).

In a multicentre, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomised to receive either abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. The duration of double-blind treatment was at least 48 weeks. In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA ≤50 copies/ml by Week 48 (point estimate for treatment difference: 0.8, 95% CI -6.3, 7.9). In the as treated (AT) analysis the difference between both treatment arms was more noticeable (88% of patients in the abacavir group, compared to 95% of patients in the zidovudine group (point estimate for treatment difference: -6.8, 95% CI -11.8; -1.7). However, both analyses were compatible with a conclusion of non-inferiority between both treatment arms.

ACTG5095 was a randomised (1:1:1), double-blind, placebo-controlled trial performed in 1147 antiretroviral naïve HIV-1 infected adults, comparing 3 regimens: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), efavirenz (EFV) vs ZDV/3TC/EFV vs ZDV/3TC/ABC. After a median follow-up of 32 weeks, the tritherapy with the three nucleosides ZDV/3TC/ABC was shown to be virologically inferior to the two other arms regardless of baseline viral load (< or > 100 000 copies/ml) with 26% of subjects on the ZDV/3TC/ABC arm, 16% on the ZDV/3TC/EFV arm and 13% on the 4 drug arm categorised as having virological failure (HIV RNA >200 copies/ml). At week 48 the proportion of subjects with HIV RNA <50 copies/ml were 63%, 80% and 86% for the ZDV/3TC/ABC, ZDV/3TC/EFV and ZDV/3TC/ABC/EFV arms, respectively. The study Data Safety Monitoring Board stopped the ZDV/3TC/ABC arm at this time based on the higher proportion of patients with virologic failure. The remaining arms were continued in a blinded fashion. After a median follow-up of 144 weeks, 25% of subjects on the ZDV/3TC/ABC/EFV arm and 26% on the ZDV/3TC/EFV arm were categorised as having virological failure. There was no significant difference in the time to first virologic failure (p=0.73, log-rank test) between the 2 arms. In this study, addition of ABC to ZDV/3TC/EFV did not significantly improve efficacy.

		ZDV/3TC/ABC	ZDV/3TC/EFV	ZDV/3TC/ABC/EFV
Virologic failure (HIV RNA >200 copies/ml)	32 weeks	26%	16%	13%
	144 weeks	-	26%	25%
Virologic success (48 weeks HIV RNA < 50 copies/ml)		63%	80%	86%

- *Therapy experienced adults*

In adults moderately exposed to antiretroviral therapy the addition of abacavir to combination antiretroviral therapy provided modest benefits in reducing viral load (median change 0.44 $\log_{10}$ copies/ml at 16 weeks).

In heavily NRTI pretreated patients the efficacy of abacavir is very low. The degree of benefit as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross-resistance to abacavir.

Once daily (600 mg) administration:

- *Therapy naïve adults*

The once daily regimen of abacavir is supported by a 48 weeks multi-centre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. These were primarily asymptomatic HIV infected patients - Centre for Disease Control and Prevention (CDC) stage A. They were randomised to receive either abacavir 600 mg once daily or 300 mg twice daily, in combination with efavirenz and lamivudine given once daily. Similar clinical success (point estimate for treatment difference -1.7, 95% CI -8.4, 4.9) was observed for both regimens. From these results, it can be concluded with 95% confidence that the true difference is no greater than 8.4% in favour of the twice daily regimen. This potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir once daily over abacavir twice daily.

There was a low, similar overall incidence of virologic failure (viral load >50 copies/ml) in both the once and twice daily treatment groups (10% and 8% respectively). In the small sample size for genotypic analysis, there was a trend toward a higher rate of NRTI-associated mutations in the once daily versus the twice daily abacavir regimens. No firm conclusion could be drawn due to the limited data derived from this study. Long term data with abacavir used as a once daily regimen (beyond 48 weeks) are currently limited.

- *Therapy experienced adults*

In study CAL30001, 182 treatment-experienced patients with virologic failure were randomised and received treatment with either the fixed-dose combination of abacavir/lamivudine (FDC) once daily or abacavir 300 mg twice daily plus lamivudine 300 mg once daily, both in combination with tenofovir and a PI or an NNRTI for 48 weeks. Results indicate that the FDC group was non-inferior to the abacavir twice daily group, based on similar reductions in HIV-1 RNA as measured by average area under the curve minus baseline (AAUCMB, -1.65 $\log_{10}$ copies/ml versus -1.83 $\log_{10}$ copies/ml respectively, 95% CI -0.13, 0.38). Proportions with HIV-1 RNA < 50 copies/ml (50% versus 47%) and < 400 copies/ml (54% versus 57%) were also similar in each group (ITT population). However, as there were only moderately experienced patients included in this study with an imbalance in baseline viral load between the arms, these results should be interpreted with caution.

In study ESS30008, 260 patients with virologic suppression on a first line therapy regimen containing abacavir 300 mg plus lamivudine 150 mg, both given twice daily and a PI or NNRTI, were randomised to continue this regimen or switch to abacavir/lamivudine FDC plus a PI or NNRTI for 48 weeks.

Results indicate that the FDC group was associated with a similar virologic outcome (non-inferior) compared to the abacavir plus lamivudine group, based on proportions of subjects with HIV-1 RNA < 50 copies/ml (90% and 85% respectively, 95% CI -2.7, 13.5).

Additional information:

The safety and efficacy of Ziagen in a number of different multidrug combination regimens is still not completely assessed (particularly in combination with NNRTIs).

Abacavir penetrates the cerebrospinal fluid (CSF) (see section 5.2), and has been shown to reduce HIV-1 RNA levels in the CSF. However, no effects on neuropsychological performance were seen when it was administered to patients with AIDS dementia complex.

Paediatric population:

A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily n/N (%)	**Once Daily n/N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/ml	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/ml	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/ml	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/ml at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/ml, <400c/ml, <1000c/ml), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

In a separate study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ≤400 copies/ml at 48 weeks, compared with those treated with lamivudine and zidovudine (47%)[p=0.09, intention to treat analysis].

Similarly, greater proportions of children treated with the abacavir containing combinations had HIV-1 RNA ≤50 copies/ml at 48 weeks (53%, 42% and 28% respectively, p=0.07).

In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/ml at Week 48. No safety concerns were observed in these subjects.

5.2 Pharmacokinetic properties

Absorption

Lamivudine and zidovudine are well absorbed from the gastrointestinal tract. The bioavailability of oral lamivudine in adults is normally between 80–85% and for zidovudine 60–70%.

A bioequivalence study compared Combivir with lamivudine 150 mg and zidovudine 300 mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. Combivir was shown to be bioequivalent to lamivudine 150 mg and zidovudine 300 mg given as separate tablets, when administered to fasting subjects.

Following single dose Combivir administration in healthy volunteers, mean (CV) lamivudine and zidovudine C_{max} values were 1.6 µg/mL (32%) and 2.0 µg/mL (40%), respectively and the corresponding values for AUC were 6.1 µg h/mL (20%) and 2.4 µg h/mL (29%) respectively. The median (range) lamivudine and zidovudine t_{max} values were 0.75 (0.50-2.00) hours and 0.50 (0.25-2.00) hours respectively. The extent of lamivudine and zidovudine absorption (AUC_{∞}) and estimates of half-life following administration of Combivir with food were similar when compared to fasting subjects, although the rates of absorption (C_{max}, t_{max}) were slowed. Based on these data Combivir may be administered with or without food.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Distribution

Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 and 1.6 l/kg respectively. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (<36% serum albumin *in vitro*). Zidovudine plasma protein binding is 34% to 38%. Interactions involving binding site displacement are not anticipated with Combivir.

Data show that lamivudine and zidovudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2-4 hours after oral administration were approximately 0.12 and 0.5 respectively. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Biotransformation

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5-10%) and low plasma binding.

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50–80% of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination

The observed lamivudine half-life of elimination is 18 to 19 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (>70%) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance ≤30 mL/min (see section 4.2).

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 l/h/kg. Renal clearance of zidovudine is estimated to be 0.34 l/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Pharmacokinetics in children

In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and at all dose levels studied in adults and children, the bioavailability was between 60-74% with a mean of 65%. Css_{max} levels were 4.45 μM (1.19 μg/mL) following a dose of 120 mg zidovudine (in solution)/m^2 body surface area and 7.7 μM (2.06 μg/mL) at 180 mg/m^2 body surface area. Dosages of 180 mg/m^2 four times daily in children produced similar systemic exposure (24 hour AUC 40.0 h μM or 10.7 h μg/mL) as doses of 200 mg six times daily in adults (40.7 h μM or 10.9 h μg/mL).

In six HIV-infected children from 2 to 13 years of age, zidovudine plasma pharmacokinetics were evaluated while subjects were receiving 120 mg/m^2 zidovudine three times daily and again after switching to 180 mg/m^2 twice daily. Systemic exposures (daily AUC and C_{max}) in plasma from the twice daily regimen appeared equivalent to those from the same total daily dose given in three divided doses [Bergshoeff, 2004].

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice a day. This dose will achieve an average AUC_{0-12} ranging from approximately 3,800 to 5,300 ng h/mL. Recent findings indicate that exposure in children <6 years of age may be reduced by about 30% compared with other age groups. Further data addressing this issue are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.

Pharmacokinetics in pregnancy

The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant women.

5.3 Preclinical safety data

The clinically relevant effects of lamivudine and zidovudine in combination are anaemia, neutropenia and leukopenia.

Mutagenicity and carcinogenicity

Neither lamivudine nor zidovudine are mutagenic in bacterial tests, but consistent with other nucleoside analogues, inhibit cellular DNA replication in *in vitro* mammalian tests such as the mouse lymphoma assay.

Lamivudine has not shown any genotoxic activity in *in vivo* studies at doses that gave plasma concentrations up to 40-50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in an oral repeated dose micronucleus test in mice. Peripheral blood lymphocytes from acquired immune deficiency syndrome (AIDS) patients receiving zidovudine treatment have also been observed to contain higher numbers of chromosome breakages.

A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested.

In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential.

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other zidovudine-related tumours observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study, by the US National Cancer Institute, zidovudine was administered at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year post-natally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment related

findings were limited to late-occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

In reproductive toxicity studies lamivudine has demonstrated evidence of causing an increase in early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of foetal abnormalities was observed at lower doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose (E460),

sodium starch glycollate,

colloidal silicon dioxide,

magnesium stearate

Tablet film coat:

Hypromellose (E464),

titanium dioxide (E171),

macrogol 400,

polysorbate 80

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Cartons containing opaque polyvinyl chloride/foil blister packs. Cartons containing white high density polyethylene (HDPE) bottle with a child-resistant closure. Each pack type contains 60 film-coated tablets.

6.6 Special precautions for disposal

No special requirements for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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